

# Prospective Randomized Trial on Radiation Dose Estimates of CT Angiography Applying Iterative Image Reconstruction

## The PROTECTION V Study



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### ABSTRACT

**OBJECTIVES** The purpose of this study was to assess the potential of iterative image reconstruction (IR) of images for radiation dose reduction in coronary computed tomography angiography (CTA). Therefore, IR in combination with 30% tube current reduction was compared with standard scanning with filtered back projection (FBP) reconstruction.

**BACKGROUND** Lately, new IR techniques with advanced raw data processing have been introduced by different computed tomography vendors, thus allowing for either image noise reduction at unchanged radiation dose levels or radiation dose reductions at comparable image noise levels.

**METHODS** In this prospective, multicenter, multivendor noninferiority trial, we randomized 400 consecutive patients to 1 of 2 groups: a control group using standard FBP image reconstruction and standard tube current or an interventional group using IR technique and 30% tube current reduction. The primary endpoint was to demonstrate noninferiority in image quality (IQ) in the IR group. IQ was assessed on a 4-point scale (1, nondiagnostic IQ; 4, excellent IQ). Secondary endpoints included total radiation dose estimates and the rate of downstream testing during 30-day follow-up.

**RESULTS** Median IQ in the IR group was noninferior compared with the conventional FBP group (IR, 3.5 [interquartile range: 3.0 to 4.0]; FBP, 3.4 [interquartile range: 2.8 to 4.0],  $p$  for noninferiority  $<0.016$ ). The radiation exposure was significantly lower in the IR group (median dose-length-product 157 [interquartile range: 114 to 239] mGy-cm vs. 222 [interquartile range: 141 to 319] mGy-cm for IR vs. FBP, respectively,  $p < 0.0001$ ). The rate of downstream testing did not differ significantly (7.7% vs. 7.9% for IR vs. FBP, respectively,  $p = 0.94$ ).

**CONCLUSIONS** Coronary CTA image quality is maintained with the combined use of a 30% reduced tube current and IR algorithms when compared with conventional FBP image reconstruction techniques and standard tube current. (Prospective Randomized Trial On Radiation Dose Estimates Of CT Angiography In Patients: [NCT01453712](https://doi.org/10.1016/j.jcmg.2015.02.024)) (J Am Coll Cardiol Img 2015;8:888-96) © 2015 by the American College of Cardiology Foundation.

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In patients with suspected coronary artery disease, coronary computed tomography angiography (CTA) is a widely used tool in daily clinical practice. Because of its high negative predictive value, it is especially useful to rule out coronary artery disease (1-4). Radiation dose associated with coronary CTA has decreased over time with appropriate dose-saving strategies such as lower tube potential imaging (100 kVp) in nonobese patients, prospectively electrocardiogram (ECG)-triggered axial image acquisition, body mass index (BMI)-tailored tube current modulation, or high-pitch helical image acquisition (4-9). However, the use of ionizing radiation remains a concern (10). Consequently, the ALARA (as low as reasonably achievable) principle demands a radiation dose as low as reasonably achievable to optimize the risk/benefit ratio (11).

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Possible strategies for radiation dose reduction are decreasing the tube current and peak tube potential. Both strategies lead to an increase in image noise that may impair diagnostic image quality (IQ). Thus, a concept to reduce image noise could be helpful to overcome those shortcomings and assist further reduce radiation dose.

Recently, new iterative image reconstruction (IR) techniques with advanced raw data processing have been introduced by different computed tomography (CT) vendors using different approaches (12-15). The concept of IR is not new and has previously been used in other diagnostic imaging modalities such as single-photon emission CT. In CT, IR helps to reduce artifacts and decrease image noise by using statistical models demanding high computed performance.

The aim of our study was to investigate the potential of IR for maintaining IQ while reducing radiation exposure in a prospective, multicenter and multivendor trial.

## METHODS

**STUDY DESIGN.** The PROTECTION V (Prospective Randomized Trial on Radiation Dose Estimates of Cardiac CT Angiography—Applying Iterative Image Reconstruction Techniques) study is an international, multicenter, multivendor investigator-driven study. In total, 400 patients were randomly

allocated at 8 study sites to either a scan protocol using IR and a 30% reduced tube current or a conventional scan protocol using filtered back projection (FBP) reconstruction and full standard tube current. Randomization of patients was executed using sealed envelopes. Patients with a stable sinus rhythm, who were more than 18 years old, and who had a clinical indication for coronary CTA on the basis of suspected coronary artery disease were included in the study. Exclusion criteria were known coronary artery disease, extensive coronary artery calcifications with an Agatston score equivalent of 800 units or higher (if calcium scoring had been performed), cardiac CTA for a noncoronary indication, and non-ECG-triggered coronary CTA studies. The study protocol was approved by the local ethics committees at each institution. Written informed consent was obtained from every patient.

The study was registered at clinicaltrials.gov (identifier [NCT01453712](#)).

**CORONARY CTA.** Coronary CTA image acquisition protocols were developed in collaboration with the local study investigators and are summarized in [Online Table 1](#). Before patient enrollment, the standard tube current settings and IR patterns were defined on the basis of the experience of the participating study investigators.

Before randomization, a localizer was acquired for planning of subsequent scan ranges, and, when indicated, a nonenhanced scan for coronary artery calcium scoring was performed. Randomization envelopes were opened before the coronary CTA to determine whether the patient was randomized to the IR or FBP group. Investigators were encouraged to use a prospectively ECG-triggered axial scan technique based on clinical appropriateness. The use of other strategies for radiation dose reduction, including ECG-controlled modulation of the tube current in retrospectively ECG-gated helical data acquisition, was recommended whenever appropriate. Automatic tube current selection was not allowed, to guarantee a 30% tube current reduction. Contrast injection protocols were carried out at the discretion of the local study investigator.

## ABBREVIATIONS AND ACRONYMS

<b>BMI</b>	= body mass index
<b>CTA</b>	= computed tomography angiography
<b>DLP</b>	= dose-length-product
<b>DSCT</b>	= dual-source computed tomography
<b>ECG</b>	= electrocardiogram
<b>FBP</b>	= filtered back projection
<b>FU</b>	= follow-up
<b>IQ</b>	= image quality
<b>IR</b>	= iterative image reconstruction

Medical Systems; and has received research grants from GE Healthcare unrelated to the current study. Dr. Chen has a research agreement with Toshiba Medical Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 16, 2014; revised manuscript received January 3, 2015, accepted February 5, 2015.

After data acquisition, the local study investigators reconstructed the images as established at the study site and as needed for clinical decision making. Images in the IR group were reconstructed using ASIR (GE Healthcare, Milwaukee, Wisconsin), iDose (Philips Healthcare, Best, the Netherlands), SAFIRE (Siemens Medical Solutions, Forchheim, Germany), and ADIR 3D (Toshiba Medical Systems, Otawara, Japan). Medium IR strength settings were recommended, but additional reconstructions at other IR strength settings were allowed for clinical decision making. Detailed IR strength settings for each vendor are presented in [Online Table 1](#). The study protocol included transmission of all available image data sets that had been acquired and reconstructed for clinical decision making to the coronary CTA core laboratory (German Heart Centre, Munich, Germany) for analysis of IQ.

**STUDY ENDPOINTS.** The primary study endpoint was diagnostic IQ, which was assessed with an established IQ score (7). Secondary endpoints included radiation exposure, vessel contour blurring (mottle score), and quantitative IQ parameters. In addition, downstream test utilization was assessed as a clinical endpoint and was evaluated by direct telephone interview. Downstream tests included stress testing (stress echocardiography, stress nuclear cardiac perfusion imaging, or stress cardiac magnetic resonance) and invasive coronary angiography within 30 days after coronary CTA.

**DATA ANALYSIS.** Data sets were evaluated in the coronary CTA core laboratory by 2 experienced readers separately in a blinded, randomized fashion. Disagreements were solved by consensus. IQ was graded on an ordinal scale ranging from 1 to 4, with 1 representing nondiagnostic, 2 adequate, 3 good, and 4 excellent IQ. Detailed information on this scoring system is described elsewhere (7). IQ was assessed for each coronary artery (left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery) and was then averaged for every patient.

The mottle score was used to assess vessel contour blurring. Contour blurring was assessed on a per-patient basis on an ordinal scale ranging from 1 to 4, which is described in detail elsewhere (8). In brief, 1 indicated extensive blurring, 2 medium blurring, 3 slight blurring, and 4 almost no or no contour blurring.

To assess quantitative IQ parameters (signal intensity, image noise, signal/noise ratio, and contrast/noise ratio), 2 circular regions of interest with a diameter of approximately 8 mm were used on reformatted

axial images with a slice thickness of 1.0 mm. The first region of interest was placed within the left ventricular cavity to obtain image signal intensity and image noise. The quotient of signal intensity and image noise was defined as signal/noise ratio. A second region of interest was placed within the left ventricular lateral wall to obtain contrast/noise ratio. Contrast/noise ratio was defined as the difference between the mean attenuation values of the left ventricular cavity and left ventricular wall, divided by image noise.

**RADIATION EXPOSURE.** The total dose-length product (DLP) was obtained for each patient and each coronary CTA. To calculate the effective dose estimate, a method proposed by the European Working Group for Guidelines on Quality Criteria in CT was used (16). The effective dose estimate is derived from the product of the DLP and a body-region conversion factor ( $k = 0.014$  mSv/mGy·cm) for the chest as the investigated anatomic region. This conversion factor is averaged between male and female models (17).

**STATISTICAL ANALYSIS.** The objective of the study was to assess the noninferiority of a reduced tube current in combination with IR compared with standard tube current combined with traditional FBP image reconstruction in terms of IQ. The assumed common SD of IQ score was 0.65 (7,8,18). Sample size calculation was on the basis of a margin of noninferiority for IQ score set at 0.25 because a larger difference has been considered clinically relevant. With a power of 90% and a 2-sided alpha level of 0.05, we estimated that 144 patients in both groups were needed to show the noninferiority of the group with reduced current and IR. Because 4 different CT manufacturers were included in the study, we aimed to include 100 patients for every CT vendor to allow for generalizable results for different CT manufacturers. Sample size calculation was performed with nQuery Advisor (Statistical Solutions, Cork, Ireland).

The analysis of primary and secondary endpoints is performed on an intention-to-diagnose basis. Results are expressed as counts (or proportions in percents) or as mean  $\pm$  SD. Radiation dose and IQ are presented as median and interquartile ranges. Continuous and categorical variables were analyzed using 2-sided Student *t* tests, chi-square tests, and Fisher exact test as appropriate. Differences in radiation dose and IQ were analyzed using the ordinal Wilcoxon rank sum test. To test for interaction related to the different IR techniques, a  $4 \times 2$  analysis of variance (ANOVA) was performed for the primary endpoint.

To test for consistency, interobserver intraclass correlation was calculated. Values  $<0.20$  were

interpreted as poor agreement, 0.21 to 0.40 as fair agreement, 0.41 to 0.60 as moderate, 0.61 to 0.80 as good, and 0.81 to 1.00 as very good agreement. For statistical analysis, BiAS version 10.12 (epsilon Verlag, Darmstadt, Germany) was used. Statistical significance was defined as a 2-sided p value <0.05.

## RESULTS

In total, 400 patients were enrolled in this study; 202 patients were randomized to the group with reduced current and IR, and 198 patients were randomized to the group with standard current and FBP. The atherosclerotic risk profile was comparable between both groups. **Table 1** shows patient and scan characteristics. Significantly more patients in the group with reduced current and IR were examined using a tube potential of 100 kVp or less (162 vs. 139,  $p < 0.01$ ). All other baseline or scan characteristics showed no significant difference.

**CORONARY CTA IMAGE QUALITY.** Median IQ scores in the IR and FBP groups were 3.5 [interquartile range: 3.0 to 4.0] and 3.4 [interquartile range: 2.8 to 4.0], respectively ( $p = 0.19$ ) (**Figure 1**). The 2-sided 95% confidence interval did not cross the pre-defined noninferiority margin of 0.25 ( $p < 0.016$ ; **Figure 1**). **Online Figure 1** illustrates the distribution of

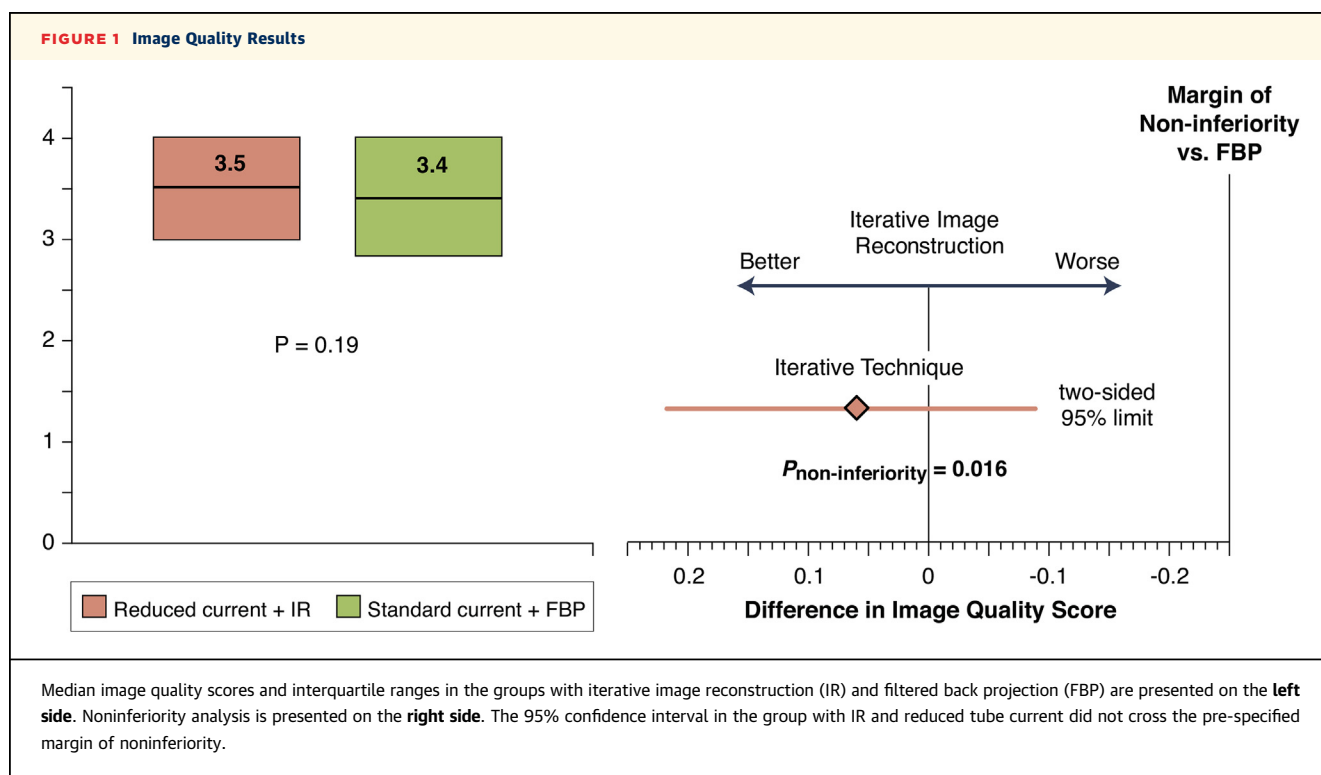
**TABLE 1 Patients and Scan Characteristics**

	Reduced Current + IR	Standard Current + FBP	p Value
Number of patients	202	198	
GE	49	47	
Philips	50	51	
Siemens	51	51	
Toshiba	52	49	
Male	129 (63.9)	123 (62.1)	0.72
Arterial hypertension	104 (51.5)	102 (51.5)	0.99
Hyperlipoproteinemia	96 (47.5)	99 (50)	0.62
Diabetes	20 (9.9)	20 (10.1)	0.95
Positive family history for CAD	69 (34.2)	69 (34.8)	0.88
Former or active smoker	71 (35.1)	66 (33.3)	0.97
Patient height, m	1.75 ± 0.33	1.75 ± 0.28	0.90
Patient weight, kg	78.6 ± 13.8	81.0 ± 19.4	0.16
BMI, kg/m <sup>2</sup>	26.3 ± 4.0	26.7 ± 5.4	0.4
Heart rate, beats/min	59.2 ± 10.8	57.5 ± 11.2	0.14
Scan length, mm	130 ± 18	129 ± 15	0.44
Tube potential = 100 kVp	162 (81)	139 (70)	0.01
Contrast volume, ml	73.1 ± 13.6	73.2 ± 14	0.89
Axial scan technique	190 (95)	185 (94.4)	0.79

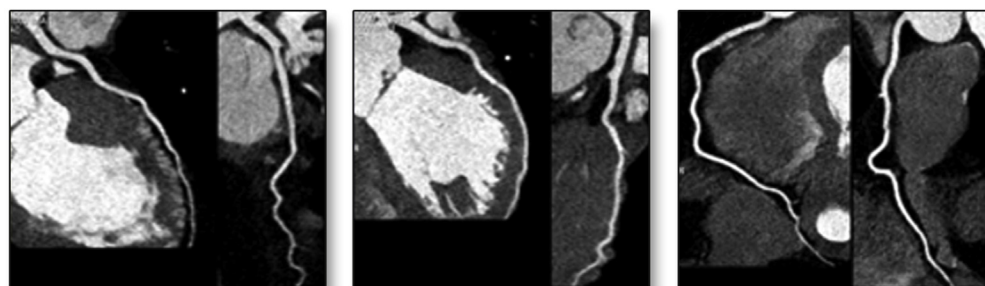
Values are n, n (%), or mean ± SD.

BMI = body mass index; CAD = coronary artery disease; FBP = filtered back projection; IR = iterative image reconstruction.

IQ in both groups. Intraclass correlation for inter-reader variability was 0.85. Representative image examples are shown in **Figure 2**. The ANOVA revealed no significant interactions ( $p = 0.65$ ).



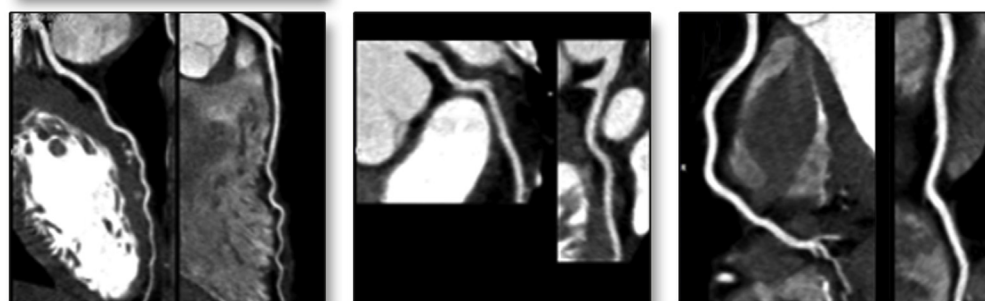
**FIGURE 2** Representative Image Examples



### Reduced Tube Current and IR

Upper row: Curved ranges of the LAD, LCx, RCA  
Lower row: Axial slice

*52 years old male patient (BMI 27.8) scanned on a Somatom Definition Flash Scanner (Siemens Healthcare) with 100 kV/258 mAs. Mean Heart Rate 53/s. DLP 256 mGy·cm (3.6 mSv).*



### Standard Tube Current and FBP

Upper row: Curved ranges of the LAD, LCx, RCA  
Lower row: Axial slice

*55 years old male patient (BMI 23.2) scanned on a Somatom Definition Flash Scanner (Siemens Healthcare) with 100 kV/370 mAs. Mean Heart Rate 66/s. DLP 324 mGy·cm (4.5 mSv).*

**Upper images** show a patient scanned with reduced tube current and iterative image reconstruction (IR). **Lower images** show a patient scanned with standard tube current and filtered back projection (FBP). DLP = dose-length-product; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

The mottle score, as a marker of vessel contour delineation, was slightly but not significantly lower in the IR group ( $3.0 \pm 0.9$  vs.  $3.1 \pm 0.9$ ,  $p = 0.27$ , respectively).

**QUANTITATIVE IMAGE QUALITY PARAMETERS.** Mean image noise was lower in the scan group with

reduced current and IR ( $28.7 \pm 8.2$  HU vs.  $30.9 \pm 12.1$  HU,  $p = 0.04$ ), whereas mean signal intensity within the left ventricular cavity was comparable ( $494 \pm 149$  HU vs.  $488 \pm 145$  HU,  $p = 0.66$ ). The resulting signal/noise and contrast/noise ratios did not differ significantly. Quantitative IQ parameters are summarized in [Table 2](#) and [Figure 3](#).



**RADIATION EXPOSURE.** Overall radiation exposure in both groups is shown in [Figure 4](#). Median DLP was significantly lower in the IR group compared with the conventional scan group (157 [114 to 239] mGy · cm vs. 222 [141 to 319] mGy · cm,  $p < 0.0001$ ). Applying the body-region conversion factor for the chest, this corresponds to an effective dose of 2.2 (1.6 to 3.3) mSv versus 3.1 (2.0 to 4.5) mSv, equalling a 29% reduction in radiation dose estimate with the use of a reduced tube current combined with IR.

**CLINICAL FOLLOW-UP.** Thirty-day clinical follow-up was completed in 387 of 400 (97%) patients ([Figure 4](#)). Six patients were lost in the IR group, and 7 patients were lost in the conventional scan group. The need for downstream testing at 30-day follow-up did not differ between both groups ( $p = 0.94$ ). During the follow-up period, 15 patients in each group underwent additional testing for suspected coronary artery disease. In the reduced IR group, all patients were referred for invasive coronary angiography. In the standard FBP scan group, 13 patients were referred for invasive coronary angiography, and 2 underwent nuclear stress testing.

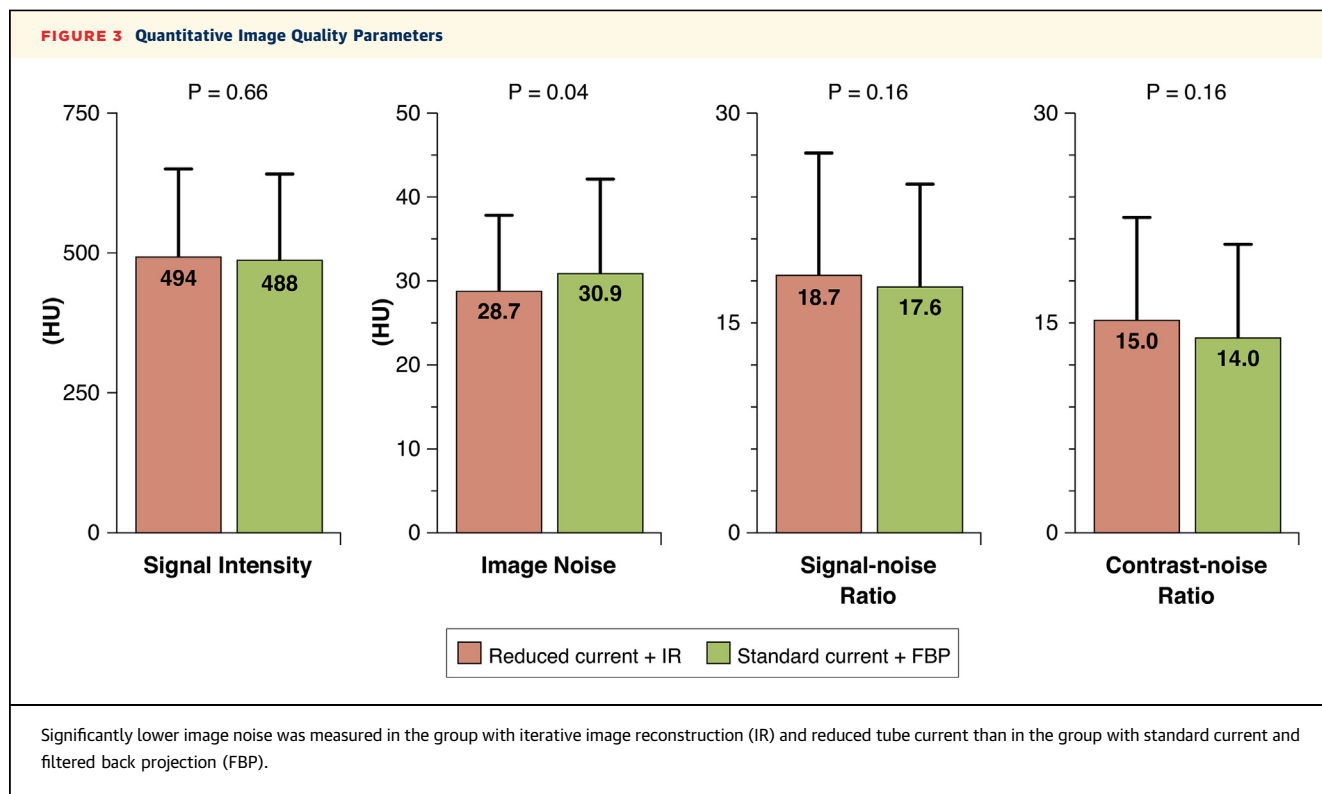
## DISCUSSION

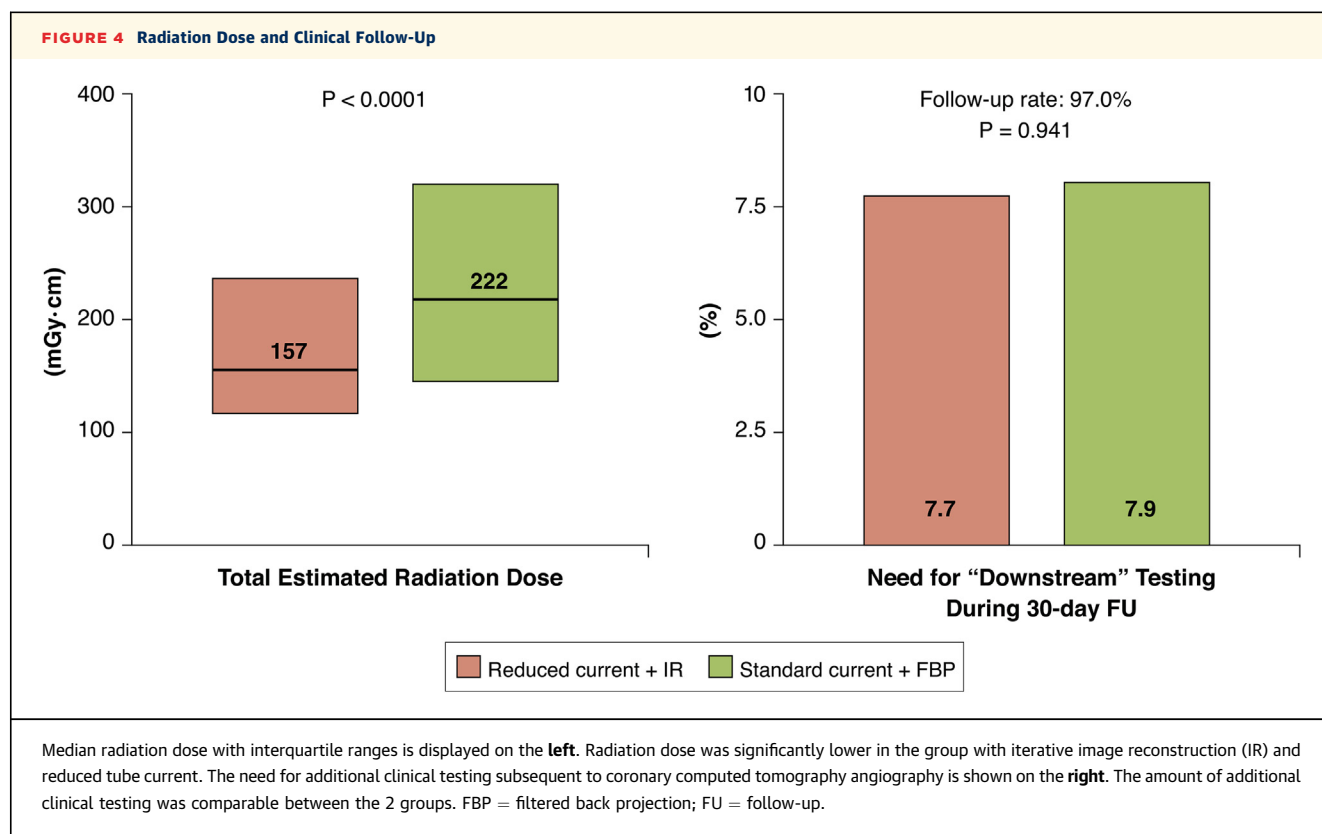
This prospective randomized, multicenter and multivendor study sought to determine whether IR

	Reduced Current + IR	Standard Current + FBP	p Value
Image quality score	3.5 (3.0–4.0)	3.4 (2.8–4.0)	0.19
GE	3.3 (2.8–3.8)	3.5 (2.8–4.0)	*
Philips	3.3 (2.8–4.0)	3.3 (2.5–3.8)	*
Siemens	4.0 (3.5–4.0)	3.5 (3.0–4.0)	*
Toshiba	3.5 (2.9–4.0)	3.3 (2.8–4.0)	*
Vessel contour blurring score	3.0 ± 0.9	3.1 ± 0.9	0.27
Patients with stenosis >50 %	44 (21.8)	41 (20.7)	0.79
Signal intensity, HU	494 ± 149	488 ± 145	0.66
Image noise, HU	28.7 ± 8.2	30.9 ± 12.1	0.04
Signal/noise ratio	18.7 ± 8.2	17.6 ± 7.4	0.16
Contrast/noise ratio	15.0 ± 7.4	14.0 ± 6.6	0.16
Dose-length-product, mGy · cm	157 (114–239)	222 (141–319)	<0.0001
GE	126 (100–252)	138 (132–265)	*
Philips	142 (103–178)	181 (139–244)	*
Siemens	230 (134–293)	319 (198–412)	*
Toshiba	159 (120–183)	237 (207–316)	*
Effective dose estimate, mSv	2.2 (1.6–3.3)	3.1 (2.0–4.5)	<0.0001
Need for additional clinical testing	15 (7.7)	15 (7.9)	0.94

Values are median (interquartile range), mean ± SD, or n (%). \*No testing for statistical significance was performed because the study was not powered for intravendor or intervendor comparisons.  
FBP = filtered back projection; IR = iterative image reconstruction.

algorithms across different scan platforms could enable comparable IQ to standard CTA with a significant reduction in radiation exposure. Our data, in fact, demonstrate a comparable and noninferior





diagnostic IQ when IR is used in combination with a 30% reduction in tube current, with radiation exposures reduced by 29% in the IR group. Importantly, although single-center validation of IR has been performed, our study is a large-scale multicenter randomized trial investigating the feasibility of a coronary CTA scan strategy that applies common IR algorithms provided by all 4 major vendors.

Coronary CTA leads to breaks in DNA double strands. Although the clinical significance of this finding is uncertain, these findings support the need for decreasing radiation dose as demanded by the ALARA principle (11,19,20). Our results could contribute to this goal in patients with a clinical indication for coronary CTA.

The principle of IR has been well described for different CT vendors (12-14,21-24). In brief, IR uses advanced computer power to overcome shortcomings associated with FBP image reconstruction algorithms. Although each vendor's approach to IR is unique, all vendors use some common principles. For example, statistical models of an ideal image and geometric models of the scanner and the x-ray tubes are implemented in image reconstruction. IR algorithms work with a "trial-and-error" approach using repetitive "correction loops" to compare the projected

images with ideal images. This approach leads to fewer artifacts and reduced image noise (25). The strength of IR is that it can be combined with other dose-saving strategies because it is incorporated in the image reconstruction process, unlike other effective dose-saving strategies such as axial or high-pitch helical image acquisition protocols. Indeed, evidence indicates that a combination of high-pitch helical image acquisition and IR can lead to radiation dose estimates lower than 0.1 mSv in carefully selected patients (26).

In our study the tube current was reduced to achieve a lower radiation dose, thus resulting in decreased density of penetrating photons. Typically, decreased photon density leads to higher image noise, which could be counterbalanced with the use of IR. Current IR algorithms allow for selecting the strength of image noise reduction; with stronger IR algorithms and more signal averaging, the reduced image noise may be associated with a "waxy" or "plastic" appearance of anatomic structures. In the current study, an intermediate strength for IR was used for image reconstruction, which resulted in an image noise that was slightly lower in the IR group without a waxy or plastic appearance of the coronary arteries when compared with the conventional group.

These results indicate that decreased photon density is well compensated for by IR at 30% tube current reduction.

**STUDY LIMITATIONS.** In the present study, the tube current was reduced by 30% and intermediate-strength IR algorithms were used. Our study does not provide information on the threshold to which the tube current can be lowered or the IR strength can be increased while IQ is maintained. A very small study published by Yin et al. (27) intraindividually compared a 50% tube current reduction and IR with a standard protocol with full tube current and FBP in 60 consecutive patients undergoing invasive coronary angiography. The receiver-operating characteristic curve showed a slightly higher diagnostic accuracy in the standard group (0.97 vs. 0.93) on a per-patient level, but those differences were not statistically significant. Results of the study by Yin et al. (27) and our study emphasize that further adequately powered randomized studies are highly desirable for each vendor to investigate how low the tube current can be set without losing diagnostic information. However, such a study would require enrollment of an unrealistically large number of patients (7). Accordingly, the current study did not investigate the noninferiority in terms of diagnostic accuracy compared with invasive coronary angiography, but rather used the IQ score as a surrogate endpoint.

Contrary to the previously mentioned study by Yin et al. (27), no intraindividual comparison was performed in our study. Instead we compared both methodologies in a clinical setting allowing for representative data evaluation. Based on the experience of previous studies, we powered this study adequately to avoid the need for repeated contrast and radiation exposure (7,8).

In the IR group, a higher percentage of patients was examined using a tube potential of 100 kVp. A lower tube potential results in higher image noise, which could impair diagnostic IQ. However, we observed a lower image noise in the IR group, and the IQ score as the primary endpoint was noninferior in the IR group.

## CONCLUSIONS

In conclusion, the PROTECTION V study demonstrates that diagnostic IQ is maintained when using IR

in combination with a 30% reduction in tube current compared with FBP and standard, clinically well-proven tube current settings. Consequently, IR should be used whenever available in pursuit of the ultimate goal to obtain diagnostic coronary CTA images with the lowest possible radiation dose. However, it is yet to be determined, to what threshold the tube current can be lowered when IR is used.

**ACKNOWLEDGMENTS** The authors highly appreciate the invaluable contributions of the co-investigators of the participating institutions: Eva Hendrich, MD, and Albrecht Will, MD (Munich, Germany); Sujata M. Shanbhag, MD, MPH, and Kathie C. Bronson, MSN, CRNP (Bethesda, Maryland); Nina Hofmann, MD, and Philipp Fortner (Heidelberg, Germany); Alessia D'Eliseo, MD (Rome, Italy); Alejandro Deviggiano, MD, and Carlos Capuñay, MD (Buenos Aires, Argentina); Michelle Williams, MD, and Edwin J. van Beek, MD (Edinburgh, United Kingdom); Patricia Bruce and Seth Kligerman, MD (Baltimore, Maryland). Patricia Bruce died in June 2014.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** This randomized, multivendor study demonstrates that diagnostic IQ in coronary CTA is maintained when modern IR algorithms are used in combination with a 30% reduction in the tube current, which translates into a reduction of radiation exposure at a comparable degree.

**TRANSLATIONAL OUTLOOK:** On the basis of the current study findings, the use of IR algorithms in combination with a reduced tube current of at least 30% is generally recommendable for coronary CTA. Future studies must determine whether the tube current can be further decreased in combination with IR.

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**KEY WORDS** computed tomography angiography, coronary, iterative image reconstruction, radiation dose

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**APPENDIX** For an additional table and figure, please see the online version of this article.